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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Paper No. 32

Application Number: 09/364,847
Filing Date: July 30, 1999
Appellant(s): PEOPLES ET AL.

Patrea L. Pabst
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed July 16, 2003.

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

A statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief.

(3) Status of Claims

The statement of the status of the claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Invention

The summary of invention contained in the brief is correct.

(6) Issues

The appellant's statement of the issues in the brief is substantially correct. The changes are as follows: Issue (2) as stated at page 3 of the appeal brief, i.e., whether claims 1-6 are clear and definite as required by 35 USC 112, second paragraph, is *not* an issue on appeal. Instead, issue (2) as listed in the appeal brief should be whether claims 1-6 are adequately described as required by 35 USC 112, first paragraph. Also, upon further consideration and in view of appellant's arguments, the scope of enablement rejection of claims 1-6 under 35 USC 112, first paragraph (Issue (1) as listed at page 3 of the appeal brief) is withdrawn. Appellant argues, "[o]ne of ordinary skill in the art... ...will understand that any/all PHA biosynthetic enzymes that fall within each of the identified classes of enzymes (based upon already known amino acid sequence and function) could be used efficiently as reagents in constructing the claimed fusions" (page 8 of the appeal brief of Paper No. 31). Thus, while the claims encompass a broad scope of individual enzymes that are fused to generate the claimed fusion protein, it is appellant's position that one of skill in the art can easily isolate those enzyme-encoding nucleic acid sequences that are not known in the art based on the sequences of known enzyme-encoding nucleic acids. Appellant

further argues, "[a]ny challenge which one of ordinary skill in the art in 1998/1999 might have encountered in attempting to make and use the claimed invention using any enzyme within the protein classes defined in claim 1 (or DNA encoding the same), could be resolved by experimentation falling short of undue" (page 8 of Paper No. 31). In view of appellant's arguments supporting a position that the entire scope of fusion enzymes can easily be constructed by the skilled artisan as evidenced by appellant's arguments at pages 6-9 of the appeal brief, such construction requiring no more than routine experimentation, the rejection is withdrawn.

The issues on appeal should appear as follows:

(1) whether claims 1-6 are adequately described as required by 35 USC 112, first paragraph;

(2) whether claims 1-3, 5, and 6 are properly rejected under 35 USC 103(a) as being obvious over Peoples et al. (US Patent 5,245,023) in view of Bulow et al. (*Trends Biotechnol* 9:226-231); and

(3) whether claim 4 is properly rejected under 35 USC 103(a) as being obvious over Peoples et al. in view of Bulow et al. as applied to claims 1-3, 5, and 6 and further in view of Argos (*J Mol Biol* 211:943-958).

(7) Grouping of Claims

Appellant's brief includes a statement that claims 1-6 do not stand or fall together and provides reasons as set forth in 37 CFR 1.192(c)(7) and (c)(8). See pages 17-18 of Paper No. 31 for those reasons wherein appellant asserts the claims do not stand or fall together. Regarding the written description rejection under 35 USC 112, first paragraph, the appellant's statement in the brief that certain claims do not stand or fall together is not agreed with because appellant has presented no argument as to why any of the dependent claims is adequately described that is independent of their arguments for the other claims. Regarding the obviousness rejection under 35 USC 103(a), the examiner has rejected the claims according to two groups – claims 1-3, 5, and 6 (Group I) and claim 4 (Group II). Appellant presents arguments as to why the claims stand or fall together at pages 17-18 of the appeal brief. Appellant's

statement in the brief that certain claims do not stand or fall together is not agreed with and appellant's arguments are addressed in the response section.

(8) Claims Appealed

The copy of the appealed claims contained in the Appendix to the brief is correct.

(9) Prior Art of Record

- Peoples et al. US Patent 5,245,023 09-1993
- Bulow et al. (1991) "Multienzyme systems obtained by gene fusion" *Trends Biotechnol* 9:226-231
- Argos (1990) "An investigation of oligopeptides linking domains in protein tertiary structures and possible candidates for general gene fusion" *J Mol Biol* 211:943-958

(10) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Written Description Rejection Under 35 USC 112, First Paragraph

Claims 1-6 are rejected under 35 USC 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 1 (claims 3-6 dependent therefrom) is directed to a fusion protein having a formula of E1-Ln-E2 or E2-Ln-E1, wherein E1 and E2 are expressed as catalytically active enzymes which act on substrate in successive reactions in a PHA biosynthetic pathway and are selected from a genus of beta-ketothiolases, acyl-CoA reductases, PHA synthases, PHB synthases, phasins, enoyl-CoA hydratases, and beta-hydroxyacyl-ACP::coenzyme-A transferases, in which linker Ln is a peptide of n amino acids that links E1 to E2. Claim 2 limits E1 and E2 of the fusion protein of claim 1 to a genus of beta-ketothiolases and acyl-CoA reductases, acyl-CoA reductases and beta-ketothiolases, PHA synthases and phasins, phasins and PHA synthases, PHA synthases and beta-hydroxyacyl-ACP::coenzyme-A transferases, beta-hydroxyacyl-ACP::coenzyme-A transferases and PHA synthases, PHA synthases and enoyl-CoA hydratases, and enoyl-CoA hydratases and PHA synthases.

The specification teaches the structures of only eight representative species of such fusion proteins, i.e., SEQ ID NO:10 (a beta-ketothiolase-acyl-CoA reductase fusion created by fusion of *A. eurtrophus* phbA and phbB genes; pages 18-22 of the specification), SEQ ID NO:19 (an acyl-CoA reductase-beta-ketothiolase fusion created by fusion of *A. eurtrophus* phbB and phbA genes; pages 23-24 of the specification), SEQ ID NO:33 (a PHA synthase-ACP::CoA transferase fusion created by fusion of *P. oleovorans* phaC and *P. putida* phaG genes; pages 24-26 of the specification), SEQ ID NO:35 (an ACP::CoA transferase-PHA synthase fusion created by fusion of *P. putida* phaG and *P. oleovorans* phaC genes; pages 24-26 of the specification), SEQ ID NO:49 (a PHA synthase-hydratase fusion created by fusion of *Z. ramigera* phaC and *A. caviae* phaJ genes; pages 26-27 of the specification), SEQ ID NO:51 (a hydratase-PHA synthase fusion created by fusion of *A. caviae* phaJ and *Z. ramigera* phaC genes; pages 26-27 of the specification), SEQ ID NO:59 (a broad substrate thiolase-reductase fusion created by fusion of *R. eutropha* bktBa and phaB genes; pages 28-29 of the specification), and SEQ ID NO:61 (a broad substrate reductase-thiolase fusion created by fusion of *R. eutropha* phaB and bktBgenes; pages 28-29 of the specification). Furthermore, the specification provides references (pages 8-11) that are asserted to disclose other naturally occurring nucleic acid sequences of genes from microorganisms encoding the enzymes recited in claims 1 and 2. It is noted that the genera of enzymes recited in the claims are not so limited to those enzymes encoded by the naturally occurring genes disclosed in the specification. Instead, the genera of enzymes as recited in claims 1 and 2 encompass species from *any* source, including species that have not been described in the specification, and further encompass mutant enzymes (see page 7, lines 22-28 of the specification) that have not been disclosed in the specification. The CAFC in *University of California v. Eli Lilly and Co.* (CAFC) 43 USPQ2d 1398 (7/22/1997) stated that:

> "[i]n claims to genetic material, however a generic statement such as 'vertebrate insulin cDNA' or 'mammalian insulin cDNA', without more, is not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus".

Similarly with the recited genera of enzymes comprising the fusion protein, the functional definition of the genus does not provide structural information commonly possessed by all members of the genus, which distinguish the enzyme species within the genus such that a skilled artisan can visualize or recognize the identity of all species of recited enzymes from *any* source. Besides the disclosed species, the specification fails to describe any other representative species of naturally occurring or mutant enzymes by any identifying characteristics or properties other than the functionality of being a fusion of the individual enzyme subunits as recited in claims 1 and 2. Based on the structures of the disclosed representative species there was (at the time of the invention), and still is, no way to predict the structures of all species of enzyme-encoding nucleic acids as encompassed by the claims, i.e., based on the structures of the representative species of enzyme-encoding nucleic acids, the structures of all species encompassed by the recited genera of enzymes is unpredictable. For inventions characterized by factors not reasonably predictable which are known to one of ordinary skill in the art, more evidence is required to show possession. Given the lack of disclosed representative species encompassed by the genera of recited enzymes, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that appellant was in possession of the claimed invention.

Rejections Under 35 USC 103(a)

I. Claims 1-3, 5, and 6 are rejected under 35 USC 103(a) as being unpatentable over Peoples et al. in view of Bulow et al. Claim 1 is drawn to a fusion protein having a formula of E1-Ln-E2 or E2-Ln-E1, wherein E1 and E2 are expressed as catalytically active enzymes which act on substrate in successive reactions in a PHA biosynthetic pathway and are selected from beta-ketothiolases, acyl-CoA reductases, PHA synthases, PHB synthases, phasins, enoyl-CoA hydratases, and beta-hydroxyacyl-ACP::coenzyme-A transferases, in which linker Ln is a peptide of n amino acids that links E1 to E2. Claim 2 limits E1 and E2 of the fusion protein of claim 1 to beta-ketothiolases and acyl-CoA reductases, acyl-CoA reductases and beta-ketothiolases, PHA synthases and phasins, phasins and PHA synthases, PHA synthases and beta-

hydroxyacyl-ACP::coenzyme-A transferases, beta-hydroxyacyl-ACP::coenzyme-A transferases and PHA synthases, PHA synthases and enoyl-CoA hydratases, and enoyl-CoA hydratases and PHA synthases. Claim 3 limits the n in the linker to between zero and fifty amino acids. Claims 5 and 6 limit the fusion protein to being expressed in a plant or bacteria, respectively.

Peoples et al. teach polyhydroxybutyrate (PHB) is a commercially useful biopolymer (column 1, lines 37-38) having a variety of potential applications, including utility as a biodegradable/thermoplastic material, as a source of chiral centers for organic syntheses, and as a matrix for drug delivery and bone replacement (column 1, lines 44-49). Peoples et al. teach there are three enzymes involved in the biosynthetic production of PHB from an acetyl-CoA precursor: beta-ketothiolase, acetoacetyl-CoA reductase, and PHB polymerase (column 1, lines 54-57). It is noted that the term "PHB polymerase" is synonymous with and is the same enzyme as "PHB synthase" as recited in the instant application. Peoples et al. teach beta-ketothiolase, acetoacetyl-CoA reductase, and PHB polymerase catalyze successive reactions in the synthesis of PHB from acetyl-CoA, i.e., beta-ketothiolase catalyzes the conversion of acetyl-CoA to acetoacetyl-CoA, which is reduced to beta-hydroxybutyryl-CoA by acetoacetyl-CoA reductase, which is the substrate for PHB polymerase (column 1, lines 63-68). Peoples et al. teach the isolation and nucleotide sequence of genes encoding beta-ketothiolase, acetoacetyl-CoA reductase, and PHB polymerase from *Zoogloea ramigera* and *Alcaligenes eutrophus* (columns 6-14 and Figures 1-4). Peoples et al. teach co-expression of beta-ketothiolase, acetoacetyl-CoA reductase, and PHB polymerase genes in *E. coli* results in the formation and accumulation of PHB (e.g., column 19, lines 36-40 and column 22, lines 18-21). Peoples et al. teach beta-ketothiolase, acetoacetyl-CoA reductase, and PHB polymerase can be co-expressed in plants and teach methods of engineering plant cells for expression of the enzymes for production of PHB (columns 26-27). Peoples et al. teach a representative example of a PHB polymerase-PHA polymerase fusion enzyme (column 23, lines 16-18). Peoples et al. do not teach a fusion of enzymes catalyzing successive enzymatic reactions, i.e., beta-ketothiolase and acetoacetyl-CoA reductase or acetoacetyl-CoA reductase and PHB polymerase.

At the time of the invention, fusion enzymes catalyzing successive enzymatic reactions were well known in the art. Bulow et al. reviews the state of the art (as of 1991) regarding multi-enzyme systems obtained by gene fusion. Bulow et al. teaches preparation of a bifunctional enzyme can be accomplished by joining the genes of two enzymes by removing the translational stop signal at the 3'-end of the first gene and ligating the ATG-start codon of the second gene in-frame with the first gene (page 227, left column). Bulow et al. continue by stating the enzyme selected to be at the N-terminal end is arbitrary and that the native tertiary structure of the fused enzymes remains almost intact (page 227, left column) and that if the entire primary sequences of the fused native enzymes are maintained in the fusion, the enzymes usually retain most of their native specific activities despite being fused together (page 230, left column). Bulow et al. teach a linker peptide of two to ten amino acids separating the fused native enzymes is optimal (page 230, left column). Bulow et al. provide two specific examples of bi-functional fusion enzymes wherein the individual enzymes of the fusion catalyze sequential reactions (page 227, right column, bottom to page 228, right column, bottom). Bulow et al. teach the advantages of fusion enzymes catalyzing successive enzymatic reactions are proximity effects (page 228, left column), i.e., wherein a substrate is transferred efficiently to a desired second enzyme instead of a competing enzyme (page 231) and an increased product formation relative to the individual native enzymes (page 228, right column).

At the time of the invention, it would have been obvious to one of ordinary skill in the art to combine the teachings of Peoples et al. and Bulow et al. for a beta-ketothiolase and acetoacetyl-CoA reductase or acetoacetyl-CoA reductase and PHB polymerase fusion protein having a linker of between two and ten amino acids expressed in *E. coli* or a plant. One would have been motivated to make a beta-ketothiolase and acetoacetyl-CoA reductase or acetoacetyl-CoA reductase and PHB polymerase fusion protein having a linker of between two and ten amino acids for expression in *E. coli* or a plant because of the teachings of Peoples et al. who teach PHB is a commercially useful biopolymer that can be expressed in bacteria or plants as described above and Bulow et al. who teach the advantages of fusion proteins, particularly those catalyzing sequential enzymatic reactions and that a linker of two to ten amino acids

separating the native enzymes is optimal as described above. One would have a reasonable expectation of success for a beta-ketothiolase and acetoacetyl-CoA reductase or acetoacetyl-CoA reductase and PHB polymerase fusion protein having a linker of between two and ten amino acids expressed in *E. coli* or a plant because of the teachings of Peoples et al. who teach the nucleotide sequences of genes encoding beta-ketothiolase, acetoacetyl-CoA reductase, and PHB polymerase and methods of isolation of these genes as described above and Bulow who teaches preparation of a fusion enzyme as described above. Therefore, claims 1-3, 5, and 6, drawn to a fusion protein as described above, would have been obvious to one of ordinary skill in the art.

II. Claim 4 is rejected under 35 USC 103(a) as being unpatentable over Peoples et al. in view of Bulow et al. as applied to claims 1-3, 5, and 6 above, and further in view of Argos. Claim 4 is drawn to the fusion protein of claim 1 with a linker comprising glycine-serine.

Peoples et al. and Bulow et al. disclose the teachings as described above. Neither Peoples et al. nor Bulow et al. teach the limitation of a linker comprising glycine-serine.

Argos teaches advantages of using an oligopeptide linker comprising glycine, serine, and threonine (page 947). Such advantages include flexibility of the linker provided by glycine due to its relatively small side chain, conformational and energetic stability due to hydrogen bonding of the polar side chain of serine and threonine with solvent in an aqueous environment and reduced susceptibility of an oligopeptide linker comprising glycine, serine, and threonine to proteolysis (page 947).

At the time of the invention, it would have been obvious to one of ordinary skill in the art to combine the teachings of Peoples et al., Bulow et al., and Argos for a beta-ketothiolase and acetoacetyl-CoA reductase or acetoacetyl-CoA reductase and PHB polymerase fusion protein having a linker of between two and ten amino acids comprising glycine-serine. One would have been motivated to make a beta-ketothiolase and acetoacetyl-CoA reductase or acetoacetyl-CoA reductase and PHB polymerase fusion protein having a linker of between two and ten amino acids comprising glycine-serine because of the teachings of Peoples et al. and Bulow et al. as described above and Argos who teaches the

advantages of using an oligopeptide comprising glycine and serine as described above. One would have a reasonable expectation of success for a beta-ketothiolase and acetoacetyl-CoA reductase or acetoacetyl-CoA reductase and PHB polymerase fusion protein having a linker of between two and ten amino acids comprising glycine-serine because of the teachings of Peoples et al., Bulow et al., and Argos. Therefore, claim 4, drawn to a fusion protein having a linker comprising glycine-serine as described above, would have been obvious to one of ordinary skill in the art.

(11) Response to Argument

Written Description Rejection Under 35 USC 112, First Paragraph

Beginning at the bottom of page 9 and continuing through to the bottom of page 12 of Paper No. 31, appellant cites the following court cases: *Vas-Cath Inc. v. Mahurkar* (CAFC) 19 USPQ2d 1111 (6/7/1991), *University of California v. Eli Lilly and Co.* (CAFC) 43 USPQ2d 1398 (7/22/1997), *Enzo Biochem Inc. v. Gen-Probe Inc.*, 63 USPQ2d 1609 (CAFC 2002), *Amgen Inc. v. Hoechst Marion Roussel Inc.*, 65 USPQ2d 1385 (CAFC 2003), and *Amgen Inc. v. Hoechst Marion Roussel Inc.*, 57 USPQ2d 1449 (DCMass 2001).

Beginning at the top of page 13 of the appeal brief, appellant argues that the USPTO has issued Guidelines that state the written description requirement can be met by a functional description of claimed materials, if coupled with a known or disclosed correlation between function and structure. Appellant argues the enzymes as recited in the claims are defined by their function and have reduced to practice all aspects required to make and use the claimed invention. Appellant's argument is not found persuasive.

While the written description requirement *can* be met by a functional description of claimed materials, if coupled with a known or disclosed correlation between function and structure, appellant has failed to demonstrate such a correlation. In this case, neither the specification nor any evidence of record suggests that there is a correlation between the function of the recited enzymes and their structures. The examiner disagrees with appellant's assertion that an enzyme's structure is defined by its function. Enzymes are *classified* according to their function, i.e., the reaction catalyzed by the enzyme. However,

an enzyme is defined primarily by its structure, which in turn determines the function of the enzyme, as acknowledged by appellant (see lines 4-7 of page 14 of Paper No. 31). The mere recitation of the name of an enzyme, which may or may not provide an indication as to the function of the enzyme, does not provide any indication as to structural features commonly possessed by members of the genus that distinguish them from others or enable one of skill in the art to visualize or recognize the identity of the members of the genus. The examiner also disagrees with appellant's assertion that all aspects required to make and use the claimed invention have been reduced to practice. As described above, the specification teaches the structures of only eight representative species of such fusion proteins, i.e., SEQ ID NO:10, 19, 33, 35, 49, 51, 59, and 61. The genera of enzymes recited in the claims are not so limited to those enzymes encoded by the genes disclosed in the specification. Instead, the genera of enzymes as recited in claims 1 and 2 encompass species from *any* source, including species that have not been described in the specification and have yet to be isolated and further encompasses mutants and variants of known and unknown enzymes (see page 7, lines 22-28 of the specification). In this case, the species disclosed in the specification fail to represent all species of enzymes as encompassed by the recited genus.

Beginning at the middle of page 13 of Paper No. 31, appellant argues the enzymes that make up each component of the fusion enzyme are well known and exist within well defined classes of proteins. Appellant argues the terms "phasins", "thiolase", "reductase", "beta-hydroxyacyl-ACP::coenzyme-A transferase", and "enoyl-CoA hydratase" classify proteins and readily convey distinguishing information concerning identity via structure and function such that a skilled artisan can easily visualize the identity of members of each classification. Appellant argues these terms are in contrast to the term "cDNA" in which one would have great difficulty in ascertaining an actual sequence and each of the above identified classes of proteins readily conveys an appropriate level structure and function, especially in view of the sequences already disclosed in the specification and known at the time of the invention. Appellant's arguments are not found persuasive.

As stated above, it is the structure, i.e., amino acid sequence, of a protein that determines its function. The examiner knows of no method of ascertaining an enzyme's structure based on the

designated name or classification given to an enzyme. In the present case, the names "phasins", "thiolase", "reductase", "beta-hydroxyacyl-ACP::coenzyme-A transferase", and "enoyl-CoA hydratase" provide no structural features commonly possessed by members of the genus that distinguish them from others or enable one of skill in the art to visualize or recognize the identity of the members of the genus and there is no evidence of record to suggest that such a relationship exists. Furthermore, while the structures of enzyme components of the fusion enzyme were known in the art at the time of the invention, the examiner knows of no method of divining the structures of other undisclosed and/or unknown members of the genus using those structures known in the art. In this case, the species disclosed in the specification fail to represent *all* species of enzymes as encompassed by the recited genus.

Beginning at the top of page 14 of Paper No. 31 appellant argues one of skill in the art will absolutely agree that functional definitions do provide structural information commonly possessed by all members of each class. Appellant argues that a protein's sequence of amino acids determines its fold, which in turn determines its function. Appellant argues that a particular function can be directly attributed to particular folds determined by specific sequences of amino acids. Appellant argues that it is well established that structure-function relationships exist and it is no more prevalent than within the enzymes recited in claim 1. Appellant argues the written description requirement can be met by a functional description of claimed materials, if coupled with a known or disclosed correlation between function and structure. Appellant's argument is not found persuasive.

The examiner agrees with appellant's assertion that the amino acid sequence of an enzyme is directly responsible for its function. However, there is simply no way of determining a structural feature – either amino acid fold or amino acid sequence - commonly possessed by members of a genus based solely on the functional definition, i.e., identifying name, of an enzyme. The recitation of "phasins", "thiolase", "reductase", "beta-hydroxyacyl-ACP::coenzyme-A transferase", and "enoyl-CoA hydratase" does not provide any information that would enable one of skill in the art to envisage the structures of members of a genus. Even if the recitation of the name of an enzyme provided information regarding the

three-dimensional fold of an enzyme – which it does not – this would not provide any further information to allow one of skill in the art to deduce the amino acid sequence of the enzyme. No method currently exists for ascertaining an enzyme's structure or commonly possessed structural features based solely on the functional definition of an enzyme.

Rejections Under 35 USC 103(a)

I. Beginning at the middle of page 14 and continuing through to the top of page 16 of Paper No. 31, appellant cites the following court cases: *In re Warner and Warner*, 154 USPQ 173 (CCPA 1967), *In re Fine* (CAFC) 5 USPQ2d 1596 (1/26/1988), *In re Dow Chemical Co.* (CAFC) 5 USPQ2d 1529 (1/25/1988), *In re Geiger* (CAFC) 2 USPQ2d 1276 (4/1/1987), *In re Lalu and Foulletier* (CAFC) 223 USPQ 1257 (11/2/1984), *In re Fritch* (CAFC) 23 USPQ2d 1780 (8/11/1992), *In re Laskowski* (CAFC) 10 USPQ2d 1397 (4/3/1989), *In re Dembiczak* (CAFC) 50 USPQ2d 1614 (4/28/1999), and *WMS Gaming Inc. v. International Game Technology* (CAFC) 51 USPQ2d 1385 (7/20/1999). Appellant argues the references must lead those in the art to what is claimed and that, in this case, there is no such teaching. Appellant's argument is not found persuasive. It is the examiner's position that the combined references of Peoples et al. and Bulow et al. render the claimed invention obvious to one of ordinary skill in the art as the cited references teach all limitations of the claimed fusion protein, provide a motivation for making the claimed fusion protein, and provide a reasonable expectation of success as described in detail below.

Beginning at the top of page 16 of Paper No. 31, appellant argues the PHA polymerase-PHB polymerase fusion protein as taught by Peoples et al. does not catalyze successive reactions in a PHA pathway, but alternative reactions. Appellant argues the fusion enzyme of Peoples et al. does not provide an indication of success for a fusion enzyme that catalyzes successive PHA biosynthetic reactions. Appellant's argument is not found persuasive. It is acknowledged that PHA polymerase and PHB polymerase of the PHA polymerase-PHB polymerase fusion enzyme of Peoples et al. (see particularly column 23, lines 16-18 of Peoples et al.) do not catalyze sequential steps of a PHA biosynthetic pathway. However, the teachings of Peoples et al. in combination with the teachings of Bulow et al. teach all

limitations of the claims, teach a motivation for constructing the claimed fusion enzyme, and provide a reasonable expectation of success for the claimed fusion enzyme as addressed in detail below.

Beginning at the bottom of page 16 of Paper No. 31, appellant argues Bulow et al. teach the optimal length of a linker peptide for the enzymes described therein, based upon correct folding and accessibility of active sites in the recombinant enzymes. Appellant argues the statements of Bulow et al. relating to enzyme technology and its usefulness in the development of metabolic engineering are entirely prophetic and that such suggestions do not create an expectation of success without evidence suggesting the fusion of enzymes catalyzing successive reactions would be successful. Appellant cites *In re O'Farrell* (CAFC) 7 USPQ2d 1673 (8/10/1988) as allegedly supporting their argument. Appellant's argument is not found persuasive. It is the examiner's position that the combined references of Peoples et al. and Bulow et al. teach all limitations of the claimed fusion protein, provide a motivation for making the claimed fusion protein and provide a *reasonable* expectation of success. Evidence of the success of generating a catalytically active fusion enzyme is provided by Bulow et al. who teach five fusion enzymes that catalyze successive enzymatic reactions and further teach that if the genes encoding the individual enzymes are fused "the enzymes usually retain most of their native specific activities despite being fused together" (page 230, left column, top). This statement is a general statement referring to *any* fusion enzyme and is not limited to those described in the reference of Bulow et al. Obviousness does *not* require absolute predictability of success (*In re O'Farrell* (CAFC) 7 USPQ2d 1673 (8/10/1988)) and, at the time of the invention, the state of the art was advanced such that a skilled artisan would have a *reasonable* expectation of success for making the claimed invention. Appellant's own statements indicate that "for one of ordinary skill in the art it is a relatively simple matter to determine whether a particular fusion, as claimed is properly functional" (page 8 of Paper No. 31) and "[a]ny challenge which one of ordinary skill in the art in 1998/1999 might have encountered in attempting to make and use the claimed invention using any enzyme within the protein classes defined in claim 1... ...could be resolved by experimentation falling short of undue" (page 8 of Paper No. 31). Furthermore, appellant has presented no objective evidence of nonobviousness. Therefore, at least in view of the teachings of Peoples et al.

providing the nucleic acid sequences of beta-ketothiolase, acetoacetyl-CoA reductase, and PHB polymerase enzymes and methods of isolation thereof from various bacterial sources, the teachings of Bulow et al. successfully demonstrating fusion enzymes that catalyze sequential enzymatic reactions and stating that "the enzymes [of a fusion enzyme] usually retain most of their native specific activities despite being fused together" (page 230, left column, top), appellant's arguments supporting the ease of creating such fusion enzymes, and appellant's failure to present objective evidence of nonobviousness, a skilled artisan would have a *reasonable* expectation of success for making the claimed fusion protein.

Beginning at the top of page 17 of Paper No. 31, appellant argues Peoples et al. teach a fusion between two equivalent enzymes, i.e., enzymes that do not catalyze successive reactions, and Bulow et al. teach peptide linkers for use in making fusion proteins. Appellant argues no evidence has been provided to suggest an expectation of success in combining/fusing two catalytically active enzymes catalyzing successive reactions in a single fusion protein. Appellant's argument is not found persuasive. As previously stated, obviousness does *not* require absolute predictability of success (*In re O'Farrell* (CAFC) 7 USPQ2d 1673 (8/10/1988)). In this case, the teachings of Peoples et al. and the state of the art relating to fusion enzymes as supported by the teachings of Bulow et al. provide the necessary evidence of a *reasonable* expectation of success for making the claimed fusion enzyme.

Beginning at the bottom of page 18 of Paper No. 31, appellant argues that at least three activities are required to successfully make and use the claimed fusion protein: proper construction at the genetic level for proper folding of each subunit, proper expression, and proper substrate/product from one enzyme domain to the next. Appellant argues the teachings of Peoples et al. and Bulow et al. do not render the claimed fusion protein obvious because successful construction and expression of a catalytically active fusion protein could not have been expected from the prior art alone and only in hindsight could an ordinarily skilled artisan have realized the claimed fusion protein. Appellant's argument is not found persuasive. Based on the teachings of the cited prior art, a skilled artisan would have had a *reasonable* expectation of success for satisfying each of appellant's required activities asserted to be required to make and use the claimed fusion protein. Regarding appellant's concerns of proper

construction and expression, Peoples et al. teach manipulation of DNA to generate recombinant DNA constructs and co-expression of beta-ketothiolase and acetoacetyl-CoA reductase in a single microorganism, techniques that were well known to one of ordinary skill in the art at the time of the invention. Furthermore, as evidenced by Bulow et al., construction of fusion enzymes was well known to one of ordinary skill in the art at the time of the invention and Bulow et al. suggests that such enzymes "usually retain most of their native specific activities despite being fused together (page 230). Neither appellant nor the prior art provides objective evidence that a skilled artisan, at the time of the invention, would not have a *reasonable* expectation of success for making the claimed fusion protein. Regarding appellant's concern of substrate/product transfer from one enzyme domain to the next, it is noted that beta-ketothiolase and acetoacetyl-CoA reductase, when co-expressed as individual enzymes along with PHB synthase, resulted in the production of PHB (column 19 of Peoples et al.), providing evidence that the product of the beta-ketothiolase enzymatic reaction was utilized by acetoacetyl-CoA reductase. Thus, one would expect that beta-ketothiolase *linked* to acetoacetyl-CoA reductase, i.e., beta-ketothiolase in even closer proximity to acetoacetyl-CoA reductase, would transfer its product to be catalyzed by acetoacetyl-CoA reductase. Neither appellant nor the prior art provides objective evidence that, at the time of the invention, the fusion enzyme as rendered obvious by Peoples et al. and Bulow et al. would not be catalytically active. Furthermore, appellant's statements would tend to support the examiner's argument that a skilled artisan would have a *reasonable* expectation of success for making the claimed fusion protein. Addressing the scope of enablement rejection, appellant argues "for one of ordinary skill in the art it is a relatively simple matter to determine whether a particular fusion, as claimed is properly functional" (page 8 of Paper No. 31) and "[a]ny challenge which one of ordinary skill in the art in 1998/1999 might have encountered in attempting to make and use the claimed invention using any enzyme within the protein classes defined in claim 1... ...could be resolved by experimentation falling short of undue" (page 8 of Paper No. 31). While the cited prior art references themselves provide sufficient guidance to make the claimed fusion protein with a *reasonable* expectation of success (as explained in detail above), appellant's own arguments indicate that construction of the claimed fusion

protein requires no more than routine experimentation, such as techniques described in Peoples et al. and Bulow et al. and well known in the art at the time of the invention.

In view of the cited references, one of ordinary skill in the art would have a reasonable expectation of success for making the claimed fusion protein. The examiner would also like to reiterate that the cited references teach all limitations of the claims and, in particular, provide a *strong* motivation for making the claimed fusion protein. Such motivation is clearly provided by Bulow et al. as stated above. Bulow et al. provide two specific examples of bi-functional fusion enzymes wherein the individual enzymes of the fusion catalyze sequential reactions and teach the advantages of fusion enzymes that catalyze successive enzymatic reactions are proximity effects and an increased product formation relative to the individual native enzymes.

Thus, the cited references teach all limitations of the claims, provide a motivation for making the claimed fusion protein, and provide a reasonable expectation of success for making the claimed fusion protein.

II. Beginning at the middle of page 17 of Paper No. 31, appellant argues the rejection of claim 4 is rendered moot in view of appellant's arguments relating to the rejection of claims 1-3, 5, and 6 as described above. Appellant's argument is not found persuasive. For those reasons set forth above and reiterated herein, the combined references of Peoples et al. and Bulow et al. render claims 1-3, 5, and 6 obvious to one of ordinary skill in the art. As stated above, in view of the teachings of Argos, Peoples et al., and Bulow et al., the fusion protein of claim 4 would have been obvious to one of ordinary skill in the art at the time of the invention.

Argument Addressing Grouping of Claims

Beginning at the bottom of page 17 of Paper No. 31, appellant argues the examiner has failed to individually examine the dependent claims. Appellant argues that each claim must be separately examined for patentability and it is not enough to examine a single independent claim and reject all

claims. Appellant argues that no rationale has been presented as to why the subject matter of claims 2, 5, and 6 is not enabled or not obvious in view of the prior art. Appellant argues claims 2, 5, and 6 must be considered separately because each group contains different elements. Appellant argues the issues of claims 2, 5, and 6 are different with regard to enabling fusion proteins wherein each enzymatic domain is different structurally and functionally (claim 2) and with regard to fusion proteins being expressed in a host cell (claims 5 and 6). Appellant argues that no prior art has been cited to show the enzymes of claim 2 or the fusion proteins expressed in a host bacterium or plant of claims 5 and 6 would be obvious to one of ordinary skill in the art. Appellant's argument is not found persuasive. The examiner FULLY disagrees with appellant's assertion that claims 2, 5, and 6 have not been separately examined. Contrary to appellant's statements, the examiner has examined ALL of claims 1-6 and provided sufficient rationale for rejecting ALL of the claims as evidenced by rejections iterated in previous Office actions. It is noted that, to the extent appellant's argument addresses the scope of enablement rejection under 35 USC 112, first paragraph, appellant's argument is rendered moot as this rejection has been withdrawn as described above. Addressing appellant's argument that the cited prior art does not teach the limitations of claims 2, it is noted that the reference of Peoples et al. teaches beta-ketothiolase and acetoacetyl-CoA reductase (an acyl-CoA reductase) polypeptides and encoding nucleic acids as recited in claim 2. Furthermore, addressing the limitations of claims 5 and 6, Peoples et al. teaches the co-expression of these enzymes in both an *E. coli* and a plant host. Thus, the teachings of Peoples et al. in combination with the reference of Bulow et al. teach all limitations of the claims and render the claimed fusion protein of claims 2, 5, and 6 obvious to one of ordinary skill in the art.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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